REMARKS/ARGUMENTS

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

Claim 1 has been amended so that the feature "ubiquitous promoter is selected from the group consisting of polymerase III dependent promoters" is replaced with "ubiquitous promoter is a polymerase-dependent H1 promoter." Basis for this amendment can be found in original claim 16.

Claim 9 has been canceled.

Claim 11 has been amended to read "inducible H1 promoter."

Claims 16 and 17 have been limited to "H1 promoter."

In claim 27, the ubiquitous promoter has been specified as a polymerase III dependent H1 promoter.

Claims 30, 31 and 36 have been limited to "H1 promoter."

Claim 31 has been made dependent on claim 30, so that it is clear that the claimed vector is suitable for introduction to the pol II locus via homologous recombination.

Applicants do not believe that any of the amendments introduce new matter. An early notice to that effect is earnestly solicited.

The Examiner should appreciate that with the proposed limitations the claims are now driven to a specific combination of promoter and locus at which the vector is

introduced. The particular combination (H1 promoter/PolII locus) is not rendered obvious by a combination of the cited references. Moreover, Applicants draw the Examiner's attention to the fact that the **H1** promoter, if introduced at a polymerase II dependent locus, possesses superior properties as compared to **U6** introduced at this locus as can be seen from the experimental portion of the present application. These superior properties would not have been expected by persons skilled in the art.

Priority

On page 11 of the amendment filed June 24, 2010, Applicants explained in detail why claims 31-34 and 36-38 were entitled to benefit of the filing date of Provisional Application Serial No. 60/485,969, filed July 10, 2003. The Examiner responds to Applicants' arguments at the top of page 3 of the final rejection that "[i]t is emphasized that prior filed application fails to disclose the chemical and physical structure of the shRNA sequence (SEQ ID NO: 23) in the claimed method of gene knock down." In response, Applicants respectfully point out that while claims 31-34 and 36-38 may generically embrace SEQ ID NO: 23, none of these claims is specifically drawn to SEQ ID NO: 23. Further, the fact that Applicants have elected to prosecute the species of SEQ ID NO: 23 does not covert any of the generic claims embracing the elected species to species claims specifically claiming that species. Consequently, Applicants do not believe that priority of these claims requires that the prior application disclose SEQ ID NO: 23. Rather, the question is whether claims 31-34 and 36-38 ***as claimed*** are supported by the prior application. Certainly, a genus can be supported by an application even though as species falling thereunder is not. Respectfully, the Examiner's position regarding priority

is in error and Applicants request that the Examiner award claims 31-34 and 36-38 benefit of the filing date of Provisional Application Serial No. 60/485,969, filed July 10, 2003.

Obviousness Rejections

Claims 31-35, 37 and 38 were rejected under 35 USC § 103(a) as being obvious over Lowe et al. ("Lowe"), US 2008/0226553, Soriano et al. ("Soriano"), US 6,461,864, and Kunath et al. ("Kunath"), *Nature Biotechnology, 21:* 559-561 (2003).

A. Claims 31-34, 37 and 38

In response, Applicants respectfully point out that Lowe's effective U.S. filing date is September 27, 2003. In contrast, as noted above, claims 31-34, 37 and 38 clearly are entitled to the benefit of Provisional Application Serial No. 60/485,969, filed July 10, 2003, which is earlier than Lowe's effective U.S. filing date. Consequently, Lowe is not prior art against these claims, and this rejection should be immediately withdrawn as to those claims.

B. Claim 35

With respect to claim 35, Applicants respectfully point out that this claim is directed to specific sequences, and there is nothing in the cited combination of references that teaches or suggests these specific sequences to persons skilled in the art. Consequently, the cited combination of references could hardly have rendered these specific sequences *prima facie* obvious to persons skilled in the art.

The Examiner responds to Applicants' arguments concerning claim 35 in the paragraph bridging pages 11-12 of the final rejection. According to the Examiner, Kunath teaches a construct comprising a RasGAP shRNA sequence having 100% sequence homology to SEQ ID NO: 23. In response, Applicants respectfully submit that this is incorrect, or at least the sequence homology is not continuous, so that Kunath does not, in fact, teach SEQ ID NO: 23. Thus, after position 14 of SEQ ID NO: 23, Kunath's sequence has **A** where SEQ ID NO: 23 has **C**; and after position 47 of SEQ ID NO: 23, Kunath's sequence has **T** where SEQ ID NO: 23 has **A**. So, the two sequences are not identical, nor has the Examiner made a case that Kunath's sequence would have rendered *prima facie* obvious SEQ ID NO: 23.

Indeed, Applicants respectfully submit that it was not obvious for a person skilled in the art that a single copy shRNA construct under the control of an RNA polymerase III (pol III) dependent H1 promoter can mediate ubiquitous RNA interference in a living organism when integrated into a RNA polymerase II (pol II) dependent locus.

None of the cited references is instructive in respect to the strategy of targeted integration of a shRNA construct under the control of a pol III dependent H1 promoter into a pol II dependent locus to achieve ubiquitous RNA interference in a living organism. Consequently, in the cited combination of references, there is a complete failure of any reasonable teaching or suggestion evidencing that a person skilled in the art had any reasonable expectation of success to express a shRNA with an ubiquitously active Pol III construct integrated into a Pol II locus. In the absence of such teaching or suggestion, Applicants respectfully submit that the cited combinations of references could have rendered any of the rejected claims *prima facie* obvious to persons skilled in the art.

Further, as noted above, the claimed invention is characterized by unexpected results, as experimental data in the specification prove the **H1** promoter, if introduced at a polymerase II dependent locus, possesses superior properties as compared to the **U6** promoter introduced at this same locus. See, for example, Example 1 and Figure 7. Applicants remind the Examiner that unexpected superiority in one arena is sufficient to support patentability. *See, for example, In re Chupp,* 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) ("Evidence that a compound is unexpectedly superior in one of a spectrum of common properties, as here, can be enough to rebut a *prima facie* case of obviousness.")

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw this rejection. An early notice that this rejection has been reconsidered and withdrawn is earnestly solicited.

Claims 1, 5, 6, 9, 10, 15, 16, 20-24, 26, 27 and 30 were rejected under 35 USC § 103(a) as being obvious over McCaffrey et al. ("McCaffrey"), *Nature, 418:* 38-39 (2002) or Beach et al. ("Beach"), US 2003/0084471, and Bronson et al. ("Bronson"), *Proc. Natl. Acad. Sci. USA 93:* 9067-9072 (1996).

Claims 1, 5, 31-34 and 36-38 were rejected under 35 USC § 103(a) as being obvious over McCaffrey or Beach and Bronson and further in view of Soriano.

Claims 11, 12 and 17 were rejected under 35 USC § 103(a) as being obvious over McCaffrey or Beach and Bronson and Soriano and further in view of Ohkawa et al. ("Ohkawa"), *Hum. Gene Ther., 11:* 577-85 (2000).

Applicants respond to the previous ***three*** obviousness rejections together, as they are all premised basely on the combination of McCaffrey or Beach and Bronson.

Applicants respectfully submit that it was not obvious for a person skilled in the art that a single copy shRNA construct under the control of an RNA polymerase III (pol III) dependent H1 promoter can mediate ubiquitous RNA interference in a living organism when integrated into a RNA polymerase II (pol II) dependent locus.

McCaffrey and Beach describe a method of gene knockdown in a mouse by administering a shRNA expression vector. However, these references are not instructive in respect to the strategy of targeted integration of a shRNA construct under the control of a pol III dependent H1 promoter into a pol II dependent locus to achieve ubiquitous RNA interference in a living organism.

McCaffrey demonstrates transient inhibition of gene expression by injection of purified siRNA or a plasmid encoding a shRNA expression vector into the tail vain of mice. Using this approach, gene knockdown is restricted to liver and persists only a few days. Although the result demonstrates that the mechanism of RNAi mediated gene silencing is functional in mice, the reference not informative in respect to transgenic shRNA expression.

On the other hand, Beach demonstrates that a luciferase specific shRNA under the control of the U6 promoter can mediate widespread gene silencing in cultured cell lines (ambiguously referred as 'in vivo' in this document). Random rather than targeted integration of shRNA expression vectors is applied in all experiments presented and the resulting cell lines were not further analyzed concerning the integration site or the number

of shRNA copies integrated into the genome. Usually, random integration of DNA vectors results in a concatameric array of multiple copies, whereas single copy integrations are unusual (Martin & Whitelaw 1996, BioAssays 18, p. 919-923). Therefore, Beach does not teach anything about the requirements of the genomic environment to facilitate transgenic shRNA expression.

The failure by Beach and McCaffrey to provide useful information concerning ubiquitous expression of shRNA transgenes in a multicellular organism is not cured by Bronson. Particularly, Bronson did not provide motivation of targeting a shRNA construct under the control of a pol III dependent H1 promoter into to a pol II dependent locus. Rather, Bronson applied homologous recombination at the HPRT locus to introduce a bcl-2 cDNA under the control of a pol II *but not* a pol III dependent H1 promoter. The expression level of the targeted bcl-2 transgenes appeared to be non-ubiquitous and varied between the two different constructs. Therefore, the data suggest that targeted integration into a ubiquitously active locus (such as hprt) does *not* support ubiquitous expression of a transgene or a shRNA under the control of a pol II dependent H1 promoter. The activity of a shRNA construct under the control of a pol III dependent H1 promoter as demonstrated by the present invention is neither taught nor suggested by the reference.

Consequently, in the cited combination of references, there is a complete failure of any reasonable teaching or suggestion evidencing that a person skilled in the art had any reasonable expectation of success to express a shRNA with an ubiquitously active Pol III construct integrated into a Pol II locus. In the absence of such teaching or suggestion, Applicants respectfully submit that none of the various cited combinations of references

could have rendered any of the rejected claims *prima facie* obvious to persons skilled in the art.

Further, as noted above, the claimed invention is characterized by unexpected results, as experimental data in the specification prove the **H1** promoter, if introduced at a polymerase II dependent locus, possesses superior properties as compared to the **U6** promoter introduced at this same locus. See again, for example, Example 1 and Figure 7. Applicants remind the Examiner that unexpected superiority in one arena is sufficient to support patentability. *See, again, for example, In re Chupp,* 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) ("Evidence that a compound is unexpectedly superior in one of a spectrum of common properties, as here, can be enough to rebut a *prima facie* case of obviousness.")

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw these three rejections. An early notice that these three rejections have been reconsidered and withdrawn is earnestly solicited.

Claims 1, 5, 6, 9-12, 15-17, 20-24, 26, 27, 37 and 38 were provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 79-82 of copending application Serial No. 11/571,194 in view of Kunath. In response, Applicants again respectfully request that this issue be held in abeyance until allowable subject matter is indicated, at which time Applicants will take appropriate action, for example, file a suitable terminal disclaimer or prove patentable distinctness.

Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,
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